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<p>(21) International Application Number: PCT/GB93/00411</p> <p>(22) International Filing Date: 26 February 1993 (26.02.93)</p> <p>(30) Priority data:</p> <table style="width: 100%; border: none;"> <tr> <td style="width: 30%;">9204577.2</td> <td style="width: 40%;">3 March 1992 (03.03.92)</td> <td style="width: 30%;">GB</td> </tr> <tr> <td>9207053.1</td> <td>31 March 1992 (31.03.92)</td> <td>GB</td> </tr> <tr> <td>9211192.1</td> <td>27 May 1992 (27.05.92)</td> <td>GB</td> </tr> </table> <p>(71) Applicant (for all designated States except US): MERCK SHARP & DOHME LIMITED [GB/GB]; Hertford Road, Hoddesdon, Hertfordshire EN11 9BU (GB).</p> <p>(72) Inventors; and</p> <p>(75) Inventors/Applicants (for US only) : LEWIS, Richard, Thomas [GB/GB]; 52 Byngams, Harlow, Essex CM19 5NS (GB). MACLEOD, Angus, Murray [GB/GB]; 24 Abbots Way, Thorley Park, Bishops Stortford, Hertfordshire CM23 4YE (GB). MERCHANT, Kevin, John [GB/GB]; 29 Red Lion Court, Dane Street, Bishops Stortford, Hertfordshire CM23 3YL (GB).</p>	9204577.2	3 March 1992 (03.03.92)	GB	9207053.1	31 March 1992 (31.03.92)	GB	9211192.1	27 May 1992 (27.05.92)	GB	<p>(74) Agent: QUILLIN, Helen, Kaye; Merck & Co., Inc., European Patent Department, Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB).</p> <p>(81) Designated States: AU, CA, JP, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).</p> <p>Published <i>With international search report.</i></p>
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<p>(54) Title: HETEROCYCLIC COMPOUNDS, PROCESSES FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM</p> <div style="text-align: center; margin: 20px 0;"> <p>(I)</p> </div>										
<p>(57) Abstract</p> <p>Compounds of formula (I), and salts and prodrugs thereof, wherein Q¹ is halo substituted phenyl; naphthyl; indolyl; benzthiophenyl; benzofuranyl; benzyl; or fluorenyl; is an optional covalent bond; one of X and Y is H and the other is hydroxy or C₁₋₆alkoxy, or X and Y are together =O or =NOR⁵; R¹ and R² are H; C₁₋₆alkyl optionally substituted by hydroxy, cyano, COR^c, CO₂R^c, CONR^cR^d, or NR^cR^d (where R^c and R^d are H, C₁₋₆ alkyl or phenyl (C₀₋₄alkyl) optionally substituted by C₁₋₆alkyl, C₁₋₆alkoxy, halo and trifluoromethyl); phenyl (C₁₋₄alkyl) (optionally substituted by C₁₋₆alkyl, C₁₋₆alkoxy, halo or trifluoromethyl); COR^c; CO₂R^c; CONR^cR^d; COC₁₋₆alkylNR^cR^d; CONR^cCOOR^d; or SO₂R^c; R³ is H, C₁₋₆alkyl or C₂₋₆alkenyl; and R⁴ is phenyl optionally substituted by C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, halo, cyano, nitro, trifluoromethyl, trimethylsilyl, OR^a, SR^a, SOR^a, NR^aR^b, NR^aCOR^b, NR^aCO₂R^b, CO₂R^a or CONR^aR^b, where R^a and R^b are H, C₁₋₆alkyl, phenyl or trifluoromethyl; are tachykinin antagonists.</p>										

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HETEROCYCLIC COMPOUNDS, PROCESSES FOR THEIR PREPARATION
AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

5 This invention relates to a class of
heterocyclic compounds which are useful as tachykinin
receptor antagonists.

 The tachykinins are a group of naturally-
occurring peptides found widely distributed throughout.
10 mammalian tissues, both within the central nervous system
and in the peripheral nervous and circulatory systems.
The structures of three known mammalian tachykinins are
as follows:

Substance P:

15 Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-NH₂

Neurokinin A:

His-Lys-Thr-Asp-Ser-Phe-Val-Gly-Leu-Met-NH₂

Neurokinin B:

Asp-Met-His-Asp-Phe-Phe-Val-Gly-Leu-Met-NH₂

20 Substance P is believed inter alia to be
involved in the neurotransmission of pain sensations
[Otsuka et al, "Role of Substance P as a Sensory
Transmitter in Spinal Cord and Sympathetic Ganglia" in
1982 Substance P in the Nervous System, Ciba Foundation
25 Symposium 91, 13-34 (published by Pitman) and Otsuka and
Yanagisawa, "Does Substance P Act as a Pain Transmitter?"
TIPS (Dec. 1987) 8 506-510], specifically in the
transmission of pain in migraine (B.E.B. Sandberg et al,
J. Med Chem, (1982) 25 1009; S. L. Shepeard et al, Br.
30 J. Pharmacol. (1993), 108, 11-12) and in arthritis
[Levine et al in Science (1984) 226 547-549]. These
peptides have also been implicated in gastrointestinal
(GI) disorders and diseases of the GI tract such as
inflammatory bowel disease [Mantyh et al in Neuroscience

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(1988) 25 (3) 817-37 and D. Regoli in "Trends in Cluster Headache" Ed. Sicuteri et al Elsevier Scientific Publishers, Amsterdam (1987) page 85)]. It is also hypothesised that there is a neurogenic mechanism for arthritis in which substance P may play a role [Kidd et al "A Neurogenic Mechanism for Symmetrical Arthritis" in The Lancet, 11 November 1989 and Grönblad et al "Neuropeptides in Synovium of Patients with Rheumatoid Arthritis and Osteoarthritis" in J. Rheumatol. (1988) 15(12) 1807-10]. Therefore, substance P is believed to be involved in the inflammatory response in diseases such as rheumatoid arthritis and osteoarthritis [O'Byrne et al in Arthritis and Rheumatism (1990) 33 1023-8]. Other disease areas where tachykinin antagonists are believed to be useful are allergic conditions [Hamelet et al Can. J. Pharmacol. Physiol. (1988) 66 1361-7], immunoregulation [Lotz et al Science (1988) 241 1218-21 and Kimball et al, J. Immunol. (1988) 141 (10) 3564-9], vasodilation, bronchospasm, reflex or neuronal control of the viscera [Mantyh et al, PNAS (1988) 85 3235-9] and, possibly by arresting or slowing β -amyloid-mediated neurodegenerative changes [Yankner et al, Science (1990) 250, 279-82], in senile dementia of the Alzheimer type, Alzheimer's disease and Down's Syndrome. Substance P may also play a role in demyelinating diseases such as multiple sclerosis and amyotrophic lateral sclerosis [J. Luber-Narod et. al., poster presented at C.I.N.P. XVIIIth Congress, 28th June-2nd July, 1992].

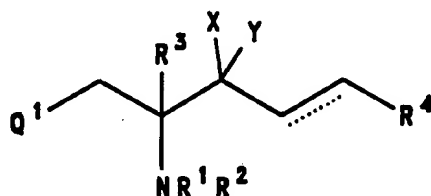
Peptide tachykinin antagonists containing an indolyl moiety are disclosed in European patent application no. 0 394 989.

In view of their metabolic instability, peptide derivatives are likely to be of limited utility as

therapeutic agents. It is for this reason that non-peptide tachykinin receptor antagonists are sought.

In essence, this invention provides a class of potent non-peptide tachykinin receptor antagonists. By virtue of their non-peptide nature, the compounds of the present invention do not suffer from the shortcomings, in terms of metabolic instability, of known peptide-based tachykinin receptor antagonists.

The present invention provides a compound of
10 formula (I), or a salt or prodrug thereof:



(1)

wherein

20 Q¹ represents a phenyl group substituted by one
or more halo; optionally substituted naphthyl; optionally
substituted indolyl; optionally substituted
benzthiophenyl; optionally substituted benzofuranyl;
optionally substituted benzyl; or optionally substituted
25 fluorenyl;

the dotted line represents an optional covalent bond;

one of X and Y represents H and the other represents hydroxy or C₁₋₆alkoxy, or X and Y together form a group =O or =NOR⁵ where R⁵ is H or C₁₋₆alkyl;

R^1 and R^2 each independently represent H;
C₁₋₆alkyl optionally substituted by hydroxy, cyano, COR^C,
CO₂R^C, CONR^CR^d, or NR^CR^d (where R^C and R^d each
independently represent H, C₁₋₆alkyl or phenyl(C₀₋₄alkyl))

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optionally substituted in the phenyl ring by one or more of C₁₋₆alkyl, C₁₋₆alkoxy, halo and trifluoromethyl); phenyl(C₁₋₄alkyl) (optionally substituted in the phenyl ring by one or more of C₁₋₆alkyl, C₁₋₆alkoxy, halo and trifluoromethyl); COR^C; CO₂R^C; CONR^CR^d; COC₁₋₆alkylNR^CR^d; 5 CONR^CCOOR^d; or SO₂R^C; where R^C and R^d are as above defined;

R³ represents H, C₁₋₆alkyl or C₂₋₆alkenyl; and R⁴ represents phenyl optionally substituted by 10 1, 2, or 3 groups selected from C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, halo, cyano, nitro, trifluoromethyl, trimethylsilyl, OR^a, SR^a, SOR^a, NR^aR^b, NR^aCOR^b, NR^aCO₂R^b, CO₂R^a or CONR^aR^b, where R^a and R^b independently represent H, C₁₋₆alkyl, phenyl or trifluoromethyl.

15 For the avoidance of doubt, when the covalent bond represented by the dotted line is present, the compounds of formula (I) contain an olefinic double bond.

As used herein, the definition of each expression, when it occurs more than once in any 20 structure, is intended to be independent of its definition elsewhere in the same structure.

Unless otherwise stated the alkyl, alkenyl and alkynyl groups referred to with respect to any of the formulae herein may represent straight, branched or 25 cyclic groups or combinations thereof. Thus, for example, suitable alkyl groups include methyl, ethyl, n- or iso-propyl, n-, sec-, iso- or tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, and cycloalkyl-alkyl groups such as cyclopropylmethyl; suitable alkenyl groups include vinyl and allyl; and suitable alkynyl 30 groups include propargyl.

The term "halo" as used herein includes fluoro, chloro, bromo and iodo, especially chloro and fluoro.

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Where Q^1 represents optionally substituted fluorenyl, the group is linked through the bridgehead carbon atom, that is to say, C-9 of the fluorenyl moiety.

Where Q^1 represents optionally substituted naphthyl, indolyl, benzothiophenyl, benzofuranyl, benzyl or fluorenyl, suitable substituents include C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, cyano, nitro, trifluoromethyl, trimethylsilyl, SR^a , SOR^a , SO_2R^a , OR^a , NR^aR^b , NR^aCOR^b , NR^aCOOR^b , $COOR^a$ or $CONR^aR^b$, where R^a and R^b are as above defined. One or more substituents may be present and each may be located at any available ring position, except, where Q^1 is optionally substituted indolyl, the nitrogen atom. Where Q^1 is optionally substituted indolyl, suitable nitrogen substituents include C_{1-6} alkyl, optionally substituted phenyl(C_{1-4} alkyl), $COOR^a$ or $CONR^aR^b$, wherein R^a and R^b are as above defined.

Suitable values of the group Q^1 include 3,4-dichlorophenyl, 3-indolyl, 2-naphthyl, 3-naphthyl, 9-fluorenyl, benzyl, 3-benzothiophenyl and 3-benzofuranyl.

Preferably Q^1 is 3-indolyl, 3-benzothiophenyl or 3,4-dichlorophenyl, more preferably 3-indolyl.

Preferably the double bond is absent.

Suitably one of X and Y represents hydroxy or C_{1-6} alkoxy, such as methoxy, or X and Y together represent =O or =NOH. Preferably one of X and Y represents methoxy, or X and Y together represent =O. More preferably X and Y together represent =O.

Suitable values for R^1 and R^2 include H, C_{1-6} alkyl, COR^c , CO_2R^c , $CONR^cR^d$ and $COC_{1-6}alkylNR^cR^d$, where R^c and R^d are as previously defined. Preferably R^1 and R^2 are selected from H, COR^c and $COC_{1-6}alkylNR^cR^d$. More preferably, one of R^1 and R^2 represents H and the other of R^1 and R^2 is selected from H, COR^{13} (where R^{13}

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is C₁₋₆alkyl, such as methyl or cyclopropyl, or phenyl(C₀₋₃alkyl), such as phenyl or phenylpropyl), or COC₁₋₆alkylN(C₁₋₆alkyl)₂. Particularly preferred are compounds wherein one of R¹ and R² represents H and the other of R¹ and R² represents CO(CH₂)_nN(CH₃)₂ where n is 3 or 4.

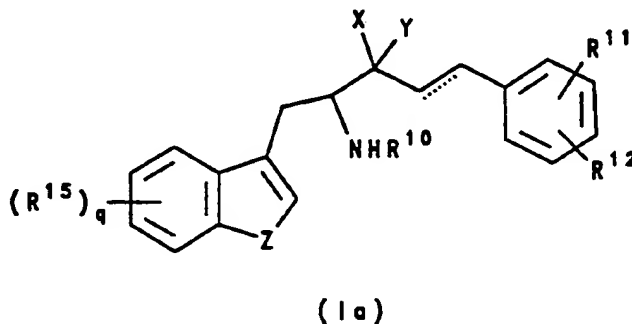
One subgroup of compounds according to the invention is represented by compounds of formula (I) wherein R³ is H or C₁₋₆alkyl.

10 Preferably R³ represents H or methyl, more preferably H.

Preferably R⁴ represents substituted phenyl. Suitable phenyl substituents include nitro, trifluoromethyl, trimethylsilyl, bromo, chloro, fluoro, iodo, cyano, methyl, ethyl, cyclopropyl, t-butyl, vinyl, methoxy, phenoxy and amino. Preferably R⁴ represents disubstituted phenyl, more preferably 3,5-disubstituted phenyl.

20 Particularly preferred are compounds wherein R⁴ represents 3,5-bis(trifluoromethyl)phenyl.

One subgroup of compounds according to the invention is represented by compounds of formula (Ia), and salts and prodrugs thereof:



wherein X and Y are as defined for formula (I);

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the dotted line represents an optional covalent bond;

Z represents O, S or NR^{14} (where R^{14} is H, C_1 -6alkyl, optionally substituted phenyl(C_1 -4alkyl), CO_2R^a or CONR^aR^b , where R^a and R^b are as previously defined), preferably S or NH;

R^{10} is H, COR^c , CO_2R^c , CONR^cR^d or COC_1 -6alkyl NR^cR^d (where R^c and R^d are as previously defined), preferably $\text{CO}(\text{C}_1$ -6alkyl) or COC_1 -6alkyl $\text{N}(\text{C}_1$ -6alkyl) $_2$;

R^{11} and R^{12} each independently represent H, C_1 -6alkyl, C_2 -6alkenyl, C_2 -6alkynyl, halo, cyano, nitro, trifluoromethyl, trimethylsilyl, OR^a , SR^a , SOR^a , NR^aR^b , NR^aCOR^b , $\text{NR}^a\text{CO}_2\text{R}^b$, CO_2R^a or CONR^aR^b , where R^a and R^b are as previously defined;

each R^{15} may occupy any available carbon atom of the bicyclic ring system and independently represents C_1 -6alkyl, C_2 -6alkenyl, C_2 -6alkynyl, halo, cyano, nitro, trifluoromethyl, trimethylsilyl, OR^a , SR^a , SOR^a , NR^aR^b , NR^aCOR^b , $\text{NR}^a\text{CO}_2\text{R}^b$, CO_2R^a or CONR^aR^b , where R^a and R^b are as previously defined; and

q is 0, 1, 2 or 3, preferably 0.

A further subgroup of compounds according to the invention is represented by compounds of formula (I) wherein Q^1 represents indolyl, benzothiophenyl or dichlorophenyl, preferably 3-indolyl, 3-benzothiophenyl or 3,4-dichlorophenyl; R^1 and R^2 are selected from H, C_1 -6alkyl, COR^c , CO_2R^c and COC_1 -6alkyl NR^cR^d ; and R^4 is 3,5-bistrifluoromethylphenyl. Preferred are compounds according to this subgroup wherein at least one of R^1 and R^2 is H.

For use in medicine, the salts of the compounds of formula (I) will be pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of

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the compounds according to the invention or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulphuric acid, oxalic acid, fumaric acid, p-toluenesulphonic acid, maleic acid, succinic acid, acetic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Salts of amine groups may also comprise quaternary ammonium salts in which the amino nitrogen atom carries a suitable organic group such as an alkyl, alkenyl, alkynyl or aralkyl moiety. Thus, for example, when both R^1 and R^2 are other than hydrogen, the nitrogen atom to which they are attached may be further substituted to give a quaternary ammonium salt. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include metal salts such as alkali metal salts, e.g. sodium or potassium salts; and alkaline earth metal salts, e.g. calcium or magnesium salts.

The present invention includes within its scope prodrugs of the compounds of formula (I) above. In general, such prodrugs will be functional derivatives of the compounds of formula (I) which are readily convertible in vivo into the required compound of formula (I). Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

The compounds according to the invention may exist both as enantiomers and as diastereomers. It is to be understood that all such isomers and mixtures thereof

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are encompassed within the scope of the present invention.

The invention also provides pharmaceutical compositions comprising one or more compounds of this invention in association with a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, solutions or suspensions, or suppositories, for oral, parenteral or rectal administration, or administration by inhalation or insufflation.

For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a non-toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage

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component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass
5 intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose
10 acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil
15 suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums
20 such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone or gelatin.

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically
25 acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as set out above. Preferably the compositions are administered by the oral or nasal respiratory route
30 for local or systemic effect. Compositions in preferably sterile pharmaceutically acceptable solvents may be nebulised by use of inert gases. Nebulised solutions may be breathed directly from the nebulising device or the nebulising device may be attached to a face mask, tent or

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intermittent positive pressure breathing machine.
Solution, suspension or powder compositions may be administered, preferably orally or nasally, from devices which deliver the formulation in an appropriate manner.

5 The present invention further provides a process for the preparation of a pharmaceutical composition comprising a compound of formula (I), which process comprises bringing a compound of formula (I) into association with a pharmaceutically acceptable carrier or
10 excipient.

 The compounds of the present invention are of value in the treatment of a wide variety of clinical conditions which are characterised by the presence of an excess of tachykinin, in particular substance P,
15 activity. These may include disorders of the central nervous system such as anxiety, depression, psychosis and schizophrenia; neurodegenerative disorders such as dementia, including senile dementia of the Alzheimer type, Alzheimer's disease and Down's syndrome;
20 demyelinating diseases such as MS and ALS and other neuropathological disorders such as peripheral neuropathy, including diabetic and chemotherapy-induced neuropathy, and postherpetic and other neuralgias; respiratory diseases, particularly those associated with
25 excess mucus secretion such as chronic obstructive airways disease, bronchopneumonia, chronic bronchitis, cystic fibrosis and asthma, and bronchospasm; inflammatory diseases such as inflammatory bowel disease, psoriasis, fibrositis, osteoarthritis and rheumatoid
30 arthritis; allergies such as eczema and rhinitis; hypersensitivity disorders such as poison ivy; ophthalmic diseases such as conjunctivitis, vernal conjunctivitis, and the like; cutaneous diseases such as contact dermatitis, atopic dermatitis, urticaria, and other

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eczematoid dermatitis; addiction disorders such as alcoholism; stress related somatic disorders; reflex sympathetic dystrophy such as shoulder/hand syndrome; dysthymic disorders; adverse immunological reactions such as rejection of transplanted tissues and disorders related to immune enhancement or suppression such as systemic lupus erythematosus; gastrointestinal (GI) disorders and diseases of the GI tract such as disorders associated with the neuronal control of viscera such as ulcerative colitis, Crohn's disease and incontinence; disorders of bladder function such as bladder detrusor hyper-reflexia; fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis; disorders of blood flow caused by vasodilation and vasospastic diseases such as angina, migraine and Reynaud's disease; and pain or nociception, for example, that attributable to or associated with any of the foregoing conditions, especially the transmission of pain in migraine. The compounds of formula (I) are particularly useful in the treatment of pain or nociception and/or inflammation and disorders associated therewith such as, for example, neuropathy, such as diabetic and chemotherapy-induced neuropathy, postherpetic and other neuralgias, asthma, osteoarthritis, rheumatoid arthritis and especially migraine.

The present invention further provides a compound of formula (I), or a salt or prodrug thereof, for use in therapy.

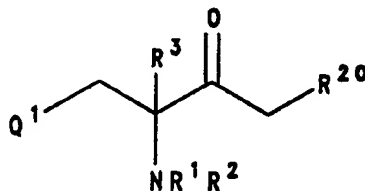
The present invention further provides a compound of formula (I) or a salt or prodrug thereof for use in the manufacture of a medicament for the treatment of physiological disorders associated with an excess of tachykinins, especially substance P.

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The present invention also provides a method for the the treatment or prevention of physiological disorders associated with an excess of tachykinins, especially substance P, which method comprises
 5 administration to a patient in need thereof of a tachykinin reducing amount of a compound or composition of this invention.

In the treatment of conditions involving actions of tachykinins released physiologically in response to noxious or other stimuli, a suitable dosage
 10 level is about 0.001 to 50 mg/kg per day, preferably about 0.005 to 10 mg/kg per day, and especially about 0.005 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day,
 15 preferably once or twice daily.

Compounds of formula (I) wherein X and Y together represent =O and the double bond is present may be prepared by reaction of an aldehyde of formula R^4CHO , wherein R^4 is as defined for formula (I) above, with a
 20 compound of formula (II):



(II)

wherein Q^1 , R^1 , R^2 and R^3 are as defined for formula (I) and R^{20} represents a group PR^X_3 or $PO(OR^X)_2$, wherein R^X
 30 represents phenyl or C_{1-10} alkyl, in the presence of a base.

Suitable bases include alkali metal hydrides, such as, for example, sodium hydride, and strong organic

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bases such as, for example, 1,8-diazabicyclo[5.4.0] undec-7-ene in the presence of anhydrous lithium chloride. Preferred bases include alkali metal carbonates such as potassium carbonate.

5 The reaction is conveniently effected in a suitable organic solvent, such as an ether, e.g. tetrahydrofuran, suitably at ambient temperature.

 The compounds of formula (I) so prepared may be converted to other compounds of formula (I) using
10 standard procedures, as follows. It is to be understood that any suitable combination of the conversion processes described may be employed in order to arrive at the desired compound of formula (I).

 Compounds of formula (I) wherein one of X and Y
15 represents H and the other represents hydroxy may be prepared from the corresponding compounds of formula (I) wherein X and Y together represent =O, by reduction.

 Suitable reducing agents include, for example, hydride reducing agents such as lithium aluminium hydride
20 and sodium borohydride.

 The reaction is conveniently carried out in a suitable organic solvent, such as an ether, e.g. tetrahydrofuran, suitably at ambient temperature.

 Compounds of formula (I) wherein one of X and Y
25 represents H and the other represents C₁₋₆alkoxy may be prepared from the corresponding compounds of formula (I) wherein one of X and Y represents H and the other represents hydroxy, by alkylation.

 Suitable alkylation procedures include
30 treatment of an alcohol of formula (I) with an alkali metal hydride, such as sodium hydride, and a C₁₋₆alkylhalide. Suitable halides include, in particular, bromides and iodides.

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The reaction is conveniently effected in an anhydrous organic solvent, for example, an ether, e.g. dimethoxyethane, suitably at ambient temperature.

Compounds of formula (I) wherein X and Y together represent =NOR^5 may be prepared from the corresponding compounds of formula (I) wherein X and Y together represent =O by the addition of hydroxylamine, or a suitable derivative thereof. Compounds wherein R^5 is other than H may be prepared from the corresponding compounds wherein R^5 is H by alkylation, for example, using a diazo compound, such as diazomethane, or an alkyl halide or sulphate.

Compounds of formula (I) wherein the double bond is absent may be prepared from the corresponding unsaturated compounds of formula (I) by reduction.

Suitable reduction procedures include catalytic hydrogenation. Suitable hydrogenation catalysts include noble metals, for example, platinum or palladium, or oxides thereof, which may be supported, for example, on charcoal. A preferred catalyst is Wilkinson's catalyst (tris(triphenylphosphine)rhodium(I)chloride).

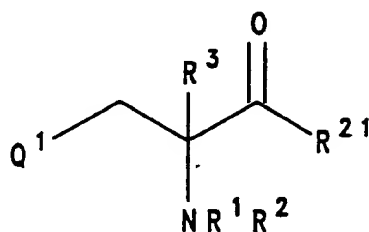
The reaction is conveniently effected in a suitable organic solvent, such as an ether, e.g. tetrahydrofuran, an alcohol, e.g. ethanol, or an ester, e.g. ethyl acetate, suitably at ambient temperature.

Compounds of formula (I) may also be prepared from different compounds of formula (I) via other suitable interconversion processes. Interconversion processes are particularly suitable for varying the substituents R^1 and R^2 . For example, compounds of formula (I), wherein one or both of R^1 and R^2 is/are other than H may be prepared from compounds of formula (I) wherein one or both of R^1 and R^2 is/are H using conventional methods, such as for example alkylation or

- 16 -

acylation. Suitable procedures will be readily apparent to those skilled in the art and are described in the accompanying examples.

Compounds of formula (II) may be prepared from
5 compounds of formula (III)



(III)

15 wherein Q^1 , R^1 , R^2 and R^3 are as defined for formula (I) and R^{21} represents an alkoxy or a suitably substituted amino group, such as a group NR^YOR^Z , where R^Y and R^Z represent alkyl, in particular a group $\text{NCH}_3(\text{OCH}_3)$; by
20 reaction with a compound of formula $\text{CH}_3\text{PO}(\text{OR}^X)_2$, where R^X is an alkyl group, in the presence of a base.

Suitable reaction procedures will be readily apparent to the skilled person and examples thereof are described in the accompanying Examples.

25 Suitable bases of use in the reaction include alkyl lithiums, such as butyl lithiums.

Compounds of formula (III) are commercially available or may be prepared using standard procedures well known to the skilled person in the art. The compounds of formula (III) are amino acid derivatives.
30 Syntheses of amino acids and derivatives thereof are well documented and are described, for example, in Chemistry and Biochemistry of the Amino Acids, ed. G. C. Barrett, Chapman and Hall, 1985.

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Where the above-described processes for the preparation of the compounds according to the invention give rise to mixtures of stereoisomers, these isomers may be separated, suitably by conventional techniques such as preparative chromatography.

The novel compounds may be prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. The novel compounds may, for example, be resolved into their component enantiomers by standard techniques, such as the formation of diastereomeric pairs by salt formation with an optically active acid, such as (-)-di-p-toluoyl-d-tartaric acid and/or (+)-di-p-toluoyl-l-tartaric acid followed by fractional crystallization and regeneration of the free base. The novel compounds may also be resolved by formation of diastereomeric esters or amides, followed by chromatographic separation and removal of the chiral auxiliary.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in Protective Groups in Organic Chemistry, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene and P.G.M. Wutts, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

The following non-limiting Examples illustrate the preparation of compounds according to the invention.

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EXAMPLE 1

2-Acetamido-1-(3-benzo[b]thienyl)-5-(3,5-bistrifluoromethylphenyl)-4-penten-3-one

5

a) 2-Acetamido-1-(3-benzo[b]thienyl)-4-diethylphosphono-3-butanone

Diethyl methyl phosphonate (13.0g) was dissolved in dry
10 tetrahydrofuran (200ml), cooled to -70°C, and treated with 1.6M
n-butyl lithium (54ml), maintaining the internal temperature at
below -60°C. The reaction mixture was stirred at -70°C for 0.5
hours before adding N-acetyl-4-(3-benzo[b]thienyl)-DL-alanine
ethyl ester (Int. J. peptide Protein Res., 29, 1987, 118-125)
15 (10.0g) in dry tetrahydrofuran (100ml). After stirring for 1.5
hours the reaction was quenched with saturated ammonium
chloride. The reaction mixture was extracted with ethyl acetate
and washed with water (3 x 50ml). The organic phase was dried
(MgSO₄), filtered and evaporated to yield an oil which was
20 purified on silica using dichloromethane/methanol (95:5) to give
the product as an oil (10.6g).

b) 2-Acetamido-1-(3-benzo[b]thienyl)-5-(3,5-bistrifluoromethylphenyl)-4-penten-3-one

25

A solution of the product of step (a) (10.6g) in dry

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tetrahydrofuran (200ml) was cooled to 0°C, treated with 60% sodium hydride in oil (1.07g) and stirred for 1 hour. 3,5-Bistrifluoromethyl benzaldehyde (6.5g) in dry tetrahydrofuran (50ml) was added dropwise to the reaction mixture which was stirred for 1 hour before quenching with saturated ammonium chloride. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 100ml). The combined organic extracts were washed with water (100ml), dried (MgSO₄), filtered and evaporated. The residue was purified by chromatography on silica using ethyl acetate/petroleum ether (bp 60-80) (2:3) to yield the title compound as a pale yellow solid (10.3g), mp = 172-173°C; found: C, 56.15; H, 3.54; N, 2.79; C₂₃H₁₇F₆NO₂S.0.25H₂O requires C, 56.38; H, 3.60; N, 2.86%.

EXAMPLE 2

2-Acetamido-1-(3-benzo[b]thienyl)-5-(3,5-bistrifluoromethylphenyl)-4-penten-3-ol

20

A solution of the product of Example 1 (2.0g) was dissolved in ethanol/dichloromethane (5:1, 100ml) and treated with sodium borohydride (0.156g). The reaction was stirred for 1 hour and then poured into water (500ml), extracted with ethyl acetate, dried (MgSO₄), filtered, and evaporated to yield an oil which was purified by chromatography on silica using ethyl acetate/petroleum ether (bp 60-80°C) to yield the title compound isomer A as a pale yellow solid (0.25g) mp = 190-191°C; found:

25

- 20 -

C, 56.19; H, 3.93; N, 2.91; $C_{23}H_{19}F_6NO_2S \cdot 0.25H_2O$ requires C, 56.15; H, 4.00; N, 2.85%.

Further elution yielded the title compound isomer B as a
5 pale yellow solid (0.5g) mp 94-95°C, found: C, 56.24; H, 4.01; N, 2.73; $C_{23}H_{19}F_6NO_2S \cdot 0.25H_2O$ requires C, 56.15; H, 4.00; N, 2.85%.

EXAMPLE 3

10

2-Acetamido-1-(3-benzo[b]thienyl)-5-(3,5-bistrifluoromethylphenyl)-3-methoxy-4-pentene

A mixture of the two isomeric alcohols of Example 2 (1.8g)
15 was dissolved in dry dimethoxyethane (25ml) and treated with sodium hydride and stirred for 10 minutes before adding iodomethane (0.2ml). The reaction was stirred for a further 0.5 hours and then quenched with saturated ammonium chloride and extracted with ethyl acetate. The separated organic layer
20 was dried ($MgSO_4$), filtered, and evaporated to yield an oil which was purified by silica chromatography using ethyl acetate/petroleum ether (bp 60-80°C), (1:1) to yield the title compound isomer A as a white solid (0.098g) mp = 125-126°C; found: C, 57.21; H, 4.33; N, 2.75; $C_{24}H_{21}F_6NO_2S$ requires C,
25 57.48; H, 4.22; N, 2.79%.

Further elution yielded the title compound isomer B as a

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white solid (0.215g), mp = 164-165°C; found: C, 57.10; H, 4.29; N, 2.76; $C_{24}H_{21}F_6NO_2S$ requires C, 57.48; H, 4.22; N, 2.79%.

EXAMPLE 4

5

2-Acetamido-1-(3-benzo[b]thienyl)-5-(3,5-bistrifluoromethylphenyl)-3-pentanone

10 2-Acetamido-1-(3-benzo[b]thienyl)-5-(3,5-bistrifluoromethylphenyl)-4-penten-3-one (2.0g) was hydrogenated in tetrahydrofuran (100ml) using 10% Pd/C (0.5g) at 50 p.s.i. The product was purified by chromatography on silica using ethyl acetate/petroleum ether (bp 60-80°C) (1:1) to yield the title compound as a white solid (1.2g), mp = 83-84°C;
15 found: C, 56.41; H, 3.81; N, 2.84; $C_{23}H_{19}F_6NO_2S$ requires C, 56.67; H, 3.93; N, 2.87%.

EXAMPLE 5

20

2-Acetamido-1-(3-benzo[b]thienyl)-5-(3,5-bistrifluoromethylphenyl)-3-pentanol

25 The compound of Example 4 (1.1g) was treated with sodium borohydride (100mg) in the same manner as Example 2 to yield the title compound isomer A as a white solid (0.23g), mp = 70-71°C; found: C, 56.43; H, 4.22; N, 2.77; $C_{23}H_{21}F_6NO_2S$ requires C, 56.44; H, 4.32; N, 2.86%.

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Further elution yielded the title compound isomer B, (0.42g), mp = 113-114°C; found: C, 56.27; H, 4.33; N, 2.81; C₂₃H₂₁F₆NO₂S requires C, 56.44; H, 4.32; N, 2.86%.

5

EXAMPLE 6

2-Acetamido-1-(3-benzo[b]thienyl)-5-(3,5-bistrifluoromethylphenyl)-3-methoxypentane

10

A mixture of the two isomeric alcohols of Example 5 (1.3g) was treated in the same manner as Example 3 to yield the title compound isomer A, 0.083g, mp = 120-121°C; found: C, 56.86; H, 4.27; N, 2.68; C₂₄H₂₃F₆NO₂S requires C, 56.74; H, 4.66; N, 2.76%.

15

Further elution yielded the title compound isomer B as a white solid (0.075g), mp = 164-166°C; found: C, 56.67; H, 4.69; N, 2.81; C₂₄H₂₃F₆NO₂S requires C, 56.74; H, 4.66; N, 2.78%.

20

EXAMPLE 7

2-Acetamido-5-(3,5-bistrifluoromethylphenyl)-1-(3-indolyl)-4-penten-3-one

25

a) Methyl 2-t-butyloxycarbonylamino-3-(3-(1-t-butyloxycarbonyl)indolyl)propionate

L-Tryptophan methyl ester hydrochloride (10g), was

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suspended in dichloromethane (200ml) and triethylamine (3.98g) was added, followed by di-t-butyl dicarbonate (8.6g). The reaction was stirred for 1 hour before adding 4-dimethyl aminopyridine (4.8g) and di-t-butyl dicarbonate (21.4g). The reaction was stirred for 16 hours and then washed with 10% citric acid (200ml), water (200ml), saturated sodium bicarbonate solution (200ml), water (200ml) and dried (MgSO_4), filtered and evaporated. The residue was purified by chromatography on silica using ethyl acetate/petroleum ether (bp 60-80°C) (1:4) to yield the title compound (13.2g).

b) 2-t-Butyloxycarbonylamino-5-(3,5-bistrifluoromethylphenyl)-1-(3-(1-t-butyloxycarbonyl)indolyl)-4-penten-3-one

The title compound was obtained by reaction of the product of part (a) by the method of Example 1.

c) 2-Acetamido-5-(3,5-bistrifluoromethylphenyl)-1-(3-indolyl)-4-penten-3-one

The product of part (b) (1.0g) was dissolved in methanolic hydrogen chloride and stirred for 16 hours. The solvent was removed and the residue was dissolved in pyridine (5ml) and acetic anhydride (1ml) was added. The reaction was stirred for 16 hours and then poured onto ice/water. The mixture was extracted with ethyl acetate (2 x 100ml) and the organic extract

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was washed with 10% citric acid (100ml), brine (100ml), saturated sodium bicarbonate (100ml), dried (MgSO_4) filtered and evaporated. The residue was purified by column chromatography on silica using isopropanol/petroleum ether (bp
5 60-80°C), (1:9), to yield the title compound as a pale yellow solid (0.35g), mp = 68-70°C; found: C, 58.23; H, 4.06; N, 5.55; $\text{C}_{23}\text{H}_{18}\text{F}_6\text{N}_2\text{O}_2 \cdot 0.25\text{H}_2\text{O}$ requires C, 58.42; H, 3.94; N, 5.92%.

EXAMPLE 8

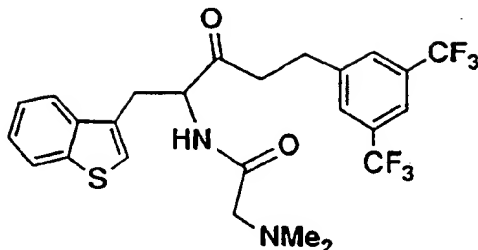
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2-Acetamido-5-(3,5-bis(trifluoromethyl)phenyl)-1-(3-indolyl)-3-pentanone

15

2-Acetamido-5-(3,5-bis(trifluoromethyl)phenyl)-1-(3-indolyl)-
4-penten-3-one (0.2g) was treated in the same manner as
Example 4 to yield the title compound as a white solid (190mg),
mp = 50-53°C; found: C, 58.69; H, 4.27; N, 5.78; $\text{C}_{23}\text{H}_{20}\text{F}_6\text{N}_2\text{O}_2$
requires C, 58.73; H, 4.29; N, 5.96%.

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EXAMPLE 9

1-(3-Benzo[b]thienyl)-5-(3,5-bistrifluoromethylphenyl)-2-
(N,N-dimethylglycinamido)-3-pentanone

(a) 3-(3-Benzo[b]thienyl)-2-t-
butyloxycarbonylaminopropionic acid

2-Amino-3-(3-benzo[b]thienyl)propionic acid (Int. J. Peptide Protein Res., (1987), 29, 118) (22.9g) and sodium carbonate (27.6g) were added to a mixture of water (350ml) and 1,4-dioxane (150ml). Di-t-butyldicarbonate (34.1g) was added to the mixture and the reaction was stirred for 16 hours and washed with ether (500ml). The reaction mixture was acidified to pH3 with solid citric acid and extracted with ethyl acetate to yield the title compound (31.5g).

(b) Methyl 3-(3-benzo[b]thienyl)-2-t-
butyloxycarbonylaminopropionate

The product of Example 9 (a) (31.5g) and Cesium carbonate (15.93g) were dissolved in methanol and the solvent was

- 26 -

removed by evaporation. The residue was dissolved in dimethylformamide and iodomethane (27.8g) was added. The reaction was stirred for 16 hours then the solvent was removed and the residue partitioned between ethyl acetate and water. The organic extract was washed with sodium bicarbonate solution and water, dried (MgSO₄), and evaporated. The residue was purified by column chromatography on silica using ethyl acetate/petroleum ether (1:4) to yield the title compound (27.3g).

(c) 1-(3-Benzo[b]thienyl)-5-(3,5-bistrifluoromethylphenyl)-2-(t-butyloxycarbonylamino)-3-pentanone

Prepared from the product of Example 9 (b) using the methods of Examples 1 and 4.

(d) 2-Amino-1-(3-benzo[b]thienyl)-5-(3,5-bistrifluoromethylphenyl)-3-pentanone hydrochloride

The product of Example 9 (c) was dissolved in methanolic hydrogen chloride and stirred for 16 hours. The solvent was removed under reduced pressure to give the title compound as a white solid.

(e) 1-(3-Benzo[b]thienyl)-5-(3,5-bistrifluoromethylphenyl)-2-(N,N-dimethylglycinamido)-3-pentanone Hydrochloride

- 27 -

N,N-Dimethyl glycine (0.206g) and triethylamine (0.5g) were dissolved in dry dimethylformamide and cooled to -30°C before adding isobutylchloroformate (0.27g). The reaction was stirred for 20 minutes before adding the product of Example 9(d). The reaction was stirred for 1 hour, poured into water and then partitioned between ethyl acetate and water. The organic phase was washed with water (100ml), sodium bicarbonate solution (100ml) and water. The organic extract was dried (MgSO₄), filtered and evaporated. The residue was purified by column chromatography on silica using ethyl acetate. The resulting oil was treated with ethereal hydrogen chloride and the solid produced after evaporation was crystallised from Et₂O/petroleum ether to give the title compound (0.36g), mp = 123-124°C; ¹H NMR (360MHz, D₆-DMSO, 300K) δ 9.02 (1H, d, J = 7Hz), 7.90-7.87 (5H, m), 7.47-7.36 (3H, m), 4.86-4.79 (1H, m), 3.98-3.79 (2H, m), 3.43-3.38 (1H, m), 3.12-2.97 (5H, m), 2.75 (3H, s), 2.64 (3H, s).

EXAMPLE 10

5-(3,5-Bistrifluoromethylphenyl)-2-t-butylloxycarbonylamino-1-(3-indolyl)-3-pentanone

(a) N-Methoxy-N-methyl 2-t-butylloxycarbonylamino-3-(3-indolyl)propionamide

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N-@-BOC-L-tryptophan (100g) was dissolved in dimethyl formamide (800ml) and triethylamine (101g) was added. The reaction was cooled to -30°C and isobutyl chloroformate (42.5ml) was added, maintaining the internal temperature to below -20°C. The reaction was stirred for 15 minutes before adding N,O-dimethyl hydroxylamine hydrochloride (64g) and then diluting the reaction with dichloromethane (1l), maintaining the internal temperature below 0°C. The reaction was stirred for 15 minutes, poured into ethyl acetate (3l) and washed with 10% citric acid (1l), water (3 x 1l), saturated sodium bicarbonate (1l) and water (1l). The organic phase was dried (MgSO₄), filtered, and evaporated until crystallisation ensued. The suspension was diluted with petroleum ether, filtered and dried to yield the title compound (90.4g); mp = 129-130°C; ¹H NMR (360MHz, D₆ DMSO) δ 10.80 (1H, s); 7.51 (1H, d, J = 7Hz); 7.33 (1H, d, J = 7Hz); 7.16 (1H, s); 7.08-6.97 (3H, m); 4.62-4.58 (1H, m); 3.72 (3H, s); 3.34 (3H, s); 3.02-2.81 (2H, m); 1.31 (9H, s).

b) 2-t-Butyloxycarbonylamino-1-(3-indolyl)-4-dimethylphosphono-3-butanone

Dimethyl methane phosphonate (205g) was dissolved in tetrahydrofuran (800ml), cooled to -70°C; and then treated with n-butyllithium (1.6M in hexane, 900ml), maintaining the internal temperature of the reaction at below -55°C. The reaction was stirred for one hour before adding the product of

- 29 -

part (a) (90g). The reaction was stirred at -70°C for 30 minutes before quenching with saturated ammonium chloride. The resulting mixture was extracted with ethyl acetate and the organic extract was washed with water (5 x 500ml), dried (MgSO₄) and evaporated. The residue was purified on silica (eluting with ethyl acetate) to yield the title compound as an oil (69.0g); ¹H NMR (360MHz, CDCl₃) δ10.84 (1H, s), 7.56 (1H, d, J = 7Hz), 7.33 (1H, d, J = 7Hz), 6.98 (1H, t, J = 7Hz), 4.34-4.31 (1H, m), 3.63 (6H, d, J = 11Hz), 3.39 (2H, d, J = 22Hz), 3.19-3.11 (1H, m), 2.91-2.84 (1H, m); found: C, 55.73, H, 6.34; N, 6.80; C₁₉H₂₇N₂O₆P requires C, 55.60; H, 6.63; N, 6.82%.

c) 5-(3,5-Bistrifluoromethylphenyl)-2-t-butyloxycarbonylamino-1-(3-indolyl)-4-penten-3-one

15

Lithium chloride (14.13g) was dried under vacuum (1mm, Hg). A solution of the product of part (b) (69.0g) in acetonitrile (600ml) was stirred with diisopropylethylamine (43.3g), and anhydrous lithium chloride (14.13g) for 30 minutes before adding 3,5-bistrifluoromethylbenzaldehyde (55g) in acetonitrile (200ml). The reaction was stirred for two hours then the solvent was removed and the residue partitioned between ethyl acetate and water. The organic phase was washed with 10% citric acid (500ml), water (500ml), saturated sodium bicarbonate (500ml) and water (500ml). The solution was dried (MgSO₄), filtered and evaporated. The residue was purified by column

25

- 30 -

chromatography on silica using ethyl acetate/petroleum ether (1:4) to yield the title compound as a pale yellow solid (77.6g), mp = 137-138°C; found: C, 59.23; H, 4.79; N, 5.35; $C_{26}H_{24}F_6N_2O_3$ requires C, 59.32; H, 4.60; N 5.32%.

5

d) 5-(3,5-Bistrifluoromethylphenyl)-2-t-butylloxycarbonylamino-1-(3-indolyl)-3-pentanone

The product of part (c) was heated under reflux with tri-n-butyltin hydride (51.12g) in toluene for 20 hours. The reaction was cooled and purified by column chromatography on silica using ethyl acetate/petroleum ether (1:4) to yield the title compound as a white solid (37.1g), mp = 138-140°C; found: C, 59.23; H, 4.90; N, 5.28; $C_{26}H_{24}F_6N_2O_3$ requires C, 59.09, H, 4.96; N, 5.30%.

15

EXAMPLE 11

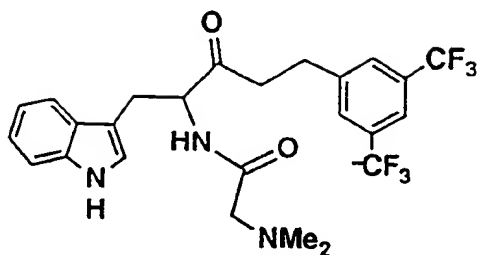
2-Amino-5-(3,5-bistrifluoromethylphenyl)-1-(3-indolyl)-3-pentanone Hydrochloride

20

The compound of Example 10 was treated in a similar manner to Example 9(d) to yield a white solid, mp = 84-86°C; found: C, 54.40; H, 4.25; N, 6.10; $C_{21}H_{18}F_6N_2O$. HCl requires C, 54.26; H, 4.12; N, 6.03%

25

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EXAMPLE 12

5-(3,5-Bis(trifluoromethyl)phenyl)-2-(N,N-dimethylglycinamido)-1-(3-indolyl)-3-pentanone Hydrochloride

Prepared from the compound of Example 11 in a similar manner to Example 9(e) to give the title compound as a white solid, mp = 194-196°C; found: C, 54.11; H, 4.65; N, 7.51; $C_{25}H_{24}F_6N_3O_2 \cdot HCl \cdot 0.25 H_2O$ requires C, 54.26; H, 4.64; N, 7.59%.

EXAMPLE 13

2-Benzamido-5-(3,5-bis(trifluoromethyl)phenyl)-1-(3-indolyl)-3-pentanone

The compound of Example 11 (0.55g) was dissolved in pyridine (10ml) and benzoyl chloride (0.17g) was added. The reaction was stirred for 16 hours and then partitioned between

- 32 -

10% citric acid (50ml) and ethyl acetate (100ml). The organic phase was washed with water (100ml) and sodium bicarbonate solution (100ml), dried (MgSO_4) and evaporated to yield an oil which was purified by chromatography on silica using petroleum ether/ethyl acetate (1:3) to yield the title compound as a white solid, mp = 119-122°C; found: C, 63.28; H, 4.25; N, 5.14; $\text{C}_{28}\text{H}_{22}\text{F}_6\text{N}_2\text{O}_2$ requires C, 63.16, H, 4.16; N, 5.26%.

EXAMPLE 14

2-Acetamido-1-(3-benzo[b]thienyl)-5-(3,5-bistrifluoromethylphenyl)-3-oximinopentane

The compound of Example 4 (0.5g) was dissolved in methanol followed by hydroxylamine hydrochloride (0.220g) and sodium acetate (0.7g). The reaction was stirred for 16 hours, the solvent was removed and the residue was dissolved in ethyl acetate (100ml), washed with water (100ml), dried (MgSO_4), filtered and evaporated to yield an oil which was purified by chromatography on silica using dichloromethane/ Et_2O (3:1) to yield the title compound isomer A as a white solid, mp = 200-201°C; found: C, 54.79; H, 4.24; N, 5.19; $\text{C}_{23}\text{H}_{20}\text{F}_6\text{N}_2\text{O}_2\text{S}$ requires C, 54.98; H, 4.01; N, 5.58%. Further elution yielded the title compound isomer B as a white solid, mp = 200-203°C; found: C, 55.13; H, 4.14; N, 5.45; $\text{C}_{23}\text{H}_{20}\text{F}_6\text{N}_2\text{O}_2\text{S}$ requires C, 54.98; H, 4.01; N, 5.58%.

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EXAMPLE 152-Acetamido-5-(3,5-bistrifluoromethylphenyl)-1-(3,4-dichlorophenyl)-3-pentanone

5

a) Diethyl (3,4-Dichlorobenzyl)acetamidomalonate

Diethyl acetamidomalonate (48.2g) was dissolved in ethanol (250ml) containing sodium ethoxide (10.2g) and stirred at room temperature for 0.5 hours before adding 3,4-dichlorobenzyl bromide and heating at reflux for 3.5 hours. After cooling, the title compound was collected by filtration and dried under reduced pressure (36.73g).

15

b) Ethyl 2-Acetamido-3-(3,4-dichlorophenyl)propionate

The product of part (a) (5g) was dissolved in ethanol and treated with sodium hydroxide (2N, 6.65ml). The reaction mixture was stirred for one hour, neutralised with hydrochloric acid and the resulting precipitate was filtered off and dissolved in 1,4 dioxan (50ml) and heated under reflux for 3 hours. The solvent was evaporated and the residue was dissolved in ethyl acetate (500ml) and washed with sodium bicarbonate (100ml) and water (100ml), dried (MgSO_4), filtered and evaporated to yield the title compound (3.0g).

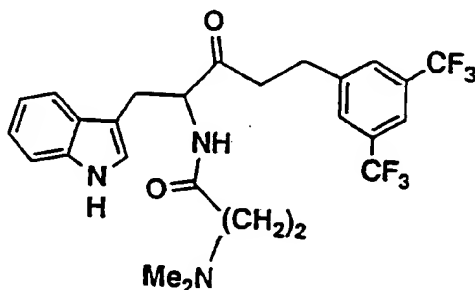
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- 34 -

c) 2-Acetamido-5-(3,5-bistrifluoromethylphenyl)-1-(3,4-dichlorophenyl)-3-pentanone

The product of part (b) was treated in the same manner as
Examples 1 and 4 to yield the title compound as a white solid,
mp = 124-126°C; found: C, 50.35; H, 3.53; N, 2.69;
C₂₁H₁₇Cl₂F₆NO₂ requires C, 50.42; H, 3.42, N, 2.80%.

EXAMPLE 16



5-(3,5-Bistrifluoromethylphenyl)-2-(3-N,N-dimethylaminopropionamido)-1-(3-indolyl)-3-pentanone Hydrochloride

Prepared by the method of Example 12 using 3-N,N-dimethylaminopropionic acid and obtained as a white solid, mp 77-80°C; found: C, 55.53; H, 5.26; N, 6.94. C₂₆H₃₀ClF₆N₃O₃ requires C, 53.66; H, 5.20; N, 7.22%.

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EXAMPLE 17

5-(3,5-Bistrifluoromethylphenyl)-2-(4-(N,N-
dimethylamino)butyramido)-1-(3-indolyl)-3-pentanone.
5 Hydrochloride

Prepared from the compound of Example 11 in a similar manner to Example 9(e) using 4-(N,N-dimethylaminobutyric acid to give the title compound as a white solid, mp 48-51°C;
10 Found: C, 54.57; H, 5.38; N, 7.23. $C_{27}H_{29}F_6N_3O_2 \cdot HCl \cdot H_2O$ requires C, 54.41; H, 5.41; N, 7.05%.

EXAMPLE 18

15 5-(3,5-Bistrifluoromethylphenyl)-2-(5-(N,N-
dimethylamino)pentanamido)-1-(3-indolyl)-3-pentanone

A solution containing the compound of Example 11 (1.1g) in dichloromethane (50ml) was treated with chloroaleryl chloride
20 (0.52ml) and triethylamine (0.64ml) for 16 hours. The reaction was diluted with dichloromethane, washed with dilute hydrochloric acid and aqueous sodium bicarbonate, dried (Na_2SO_4) and concentrated to give an oil. To a solution containing the forgoing oil in ethanol (5ml) was added
25 dimethylamine (5ml of a 33% solution in ethanol) and potassium iodide (50mg). After stirring for 4 days the mixture was partitioned between ethyl acetate and water. The ethyl acetate solution was separated, dried and concentrated and the residue

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purified by chromatography on silica gel eluting with ethyl acetate-methanol (95:5) to give the title compound, mp 140°C; found: C, 59.31; H, 5.47; N, 7.37. $C_{28}H_{31}F_6N_3O \cdot 0.5H_2O$ requires: C, 59.57; H, 5.71; N, 7.44.

5

EXAMPLE 19

5-(3,5-Bistrifluoromethylphenyl)-2-(cyclopropylcarboxamido)-1-(3-indolyl)-3-pentanone

10

To a solution of 4-bromobutyryl chloride (0.4g) and triethylamine (0.61ml) in dichloromethane (20ml) was added the compound of Example 11 (1.0g). After stirring for 16 hours the solution was washed with water, dried (Na_2SO_4) and concentrated. Chromatography on silica gel eluting with ethyl acetate/petroleum ether followed by crystallisation from diethyl ether/petroleum ether gave the title compound, mp 142-145°C: found: C, 60.66; H, 4.46; N, 5.59. $C_{25}H_{22}F_6N_2O_2$ requires C, 60.48; H, 4.47; N, 5.64.

15

20

EXAMPLE 20

5-(3,5-Bistrifluoromethylphenyl)-2-(3-phenylbutyramido)-1-(3-indolyl)-3-pentanone

25

Prepared by the method of Example 20 using phenyl butyric acid and omitting the final lithium hydroxide hydrolysis. Mp

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133-137°C; found: C, 64.76; H, 4.87; N, 4.72. $C_{31}H_{28}F_6N_2O_2$
requires C, 64.80; H, 4.91; N, 4.88.

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The following examples illustrate pharmaceutical compositions according to the invention.

EXAMPLE 21A Tablets containing 1-25mg of compound

5		<u>Amount mg</u>		
	Compound of formula (I)	1.0	2.0	25.0
	Microcrystalline cellulose	20.0	20.0	20.0
	Modified food corn starch	20.0	20.0	20.0
	Lactose	58.5	57.5	34.5
10	Magnesium Stearate	0.5	0.5	0.5

EXAMPLE 21B Tablets containing 26-100mg of compound

		<u>Amount mg</u>		
	Compound of formula (I)	26.0	50.0	100.0
15	Microcrystalline cellulose	80.0	80.0	80.0
	Modified food corn starch	80.0	80.0	80.0
	Lactose	213.5	189.5	139.5
	Magnesium Stearate	0.5	0.5	0.5
20	The compound of formula (I), cellulose, lactose and a portion of the corn starch are mixed and granulated with 10% corn starch paste. The resulting granulation is sieved, dried and blended with the remainder of the corn starch and the magnesium stearate. The resulting granulation is then compressed into tablets containing			
25	1.0mg, 2.0mg, 25.0mg, 26.0mg, 50.0mg and 100mg of the active compound per tablet.			

EXAMPLE 22 Parenteral injection

		<u>Amount mg</u>
30	Compound of formula (I)	1 to 100mg
	Citric Acid Monohydrate	0.75mg
	Sodium Phosphate	4.5mg
	Sodium Chloride	9mg
	Water for Injections	to 1ml

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The sodium phosphate, citric acid monohydrate and sodium chloride are dissolved in a portion of the water. The compound of formula (I) is dissolved or suspended in the solution and made up to volume.

5

EXAMPLE 23 Topical formulation

	<u>Amount mg</u>
Compound of formula (I)	1-10g
Emulsifying Wax	30g
10 Liquid paraffin	20g
White Soft Paraffin	to 100g

The white soft paraffin is heated until molten. The liquid paraffin and emulsifying wax are incorporated and stirred until dissolved. The compound of formula (I) is added and stirring continued until dispersed. The mixture is then cooled until solid.

15

SUBSTANCE P ANTAGONISM ASSAY

- 20 A. Receptor Expression in Monkey Kidney Cell Line (COS)
To express the cloned human neurokinin-1- receptor (NK1R) transiently in COS, the cDNA for the human NK1R was cloned into the expression vector pCDM9 which was derived from pCDM8 (INVITROGEN) by inserting the
25 ampicillin resistance gene (nucleotide 1973 to 2964 from BLUESCRIPT SK+ (trademark, STRATAGENE, La Jolla, CA, USA)) into the Sac II site. Transfection of 20 ug of the plasmid DNA into 10 million COS cells was achieved by electroporation in 800 µl of transfection buffer (135 mM
30 NaCl, 1.2 mM CaCl₂, 1.2 mM MgCl₂, 2.4 mM K₂HPO₄, 0.6 mM KH₂PO₄, 10 mM glucose, 10 mM N-2-hydroxyethyl-piperazine-N'-2-ethane sulphonic acid (HEPES) pH 7.4) at 260 V and 950 µF using the IBI GENEZAPPER (trademark IBI, New Haven, CT, USA). The cells were incubated in 10% fetal

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calf serum, 2 mM glutamine, 100U/ml penicillin-streptomycin, and 90% DMEM media (GIBCO, Grand Island, NY, USA) in 5% CO₂ at 37°C for three days before the binding assay.

5

B. Stable Expression in Chinese Hamster Ovarian Cell Line (CHO)

To establish a stable cell line expressing cloned human NK1R, the cDNA was subcloned into the vector pRcCMV (INVITROGEN). Transfection of 20 µg of the plasmid DNA into CHO cells was achieved by electroporation in 800 µl of transfection buffer supplemented with 0.625 mg/ml Herring sperm DNA at 300 V and 950 µF using the IBI GENEZAPPER (IBI). The transfected cells were incubated in CHO media [10% fetal calf serum, 100 U/ml penicillin-streptomycin, 2 mM glutamine, 1/500 hypoxanthine-thymidine (ATCC), 90% IMDM media (JRH BIOSCIENCES, Lenexa, KS, USA), 0.7 mg/ml G418 (GIBCO)] in 5% CO₂ at 37°C until colonies were visible. Each colony was separated and propagated. The cell clone with the highest number of human NK1R was selected for subsequent applications such as drug screening.

C. Assay Protocol using COS or CHO

The binding assay of human NK1R expressed in either COS or CHO cells is based on the use of ¹²⁵I-substance P (¹²⁵I-SP, from DU PONT, Boston, MA) as a radioactively labeled ligand which competes with unlabeled substance P or any other ligand for binding to the human NK1R. Monolayer cell cultures of COS or CHO were dissociated by the non-enzymatic solution (SPECIALTY MEDIA, Lavellette, NJ) and resuspended in appropriate volume of the binding buffer (50 mM Tris pH 7.5, 5 mM MnCl₂, 150 mM NaCl, 0.04 mg/ml bacitracin, 0.004 mg/ml leupeptin, 0.2 mg/ml BSA,

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0.01 mM phosphoramidon) such that 200 μ l of the cell suspension would give rise to about 10,000 cpm of specific ^{125}I -SP binding (approximately 50,000 to 200,000 cells). In the binding assay, 200 μ l of cells were added to a tube containing 20 μ l of 1.5 to 2.5 nM of ^{125}I -SP and 20 μ l of unlabeled substance P or any other test compound. The tubes were incubated at 4°C or at room temperature for 1 hour with gentle shaking. The bound radioactivity was separated from unbound radioactivity by GF/C filter (BRANDEL, Gaithersburg, MD) which was pre-wetted with 0.1% polyethylenimine. The filter was washed with 3 ml of wash buffer (50 mM Tris pH 7.5, 5 mM MnCl_2 , 150 mM NaCl) three times and its radioactivity was determined by gamma counter.

The activation of phospholipase C by NK1R may also be measured in CHO cells expressing the human NK1R by determining the accumulation of inositol monophosphate which is a degradation product of IP_3 . CHO cells are seeded in 12-well plate at 250,000 cells per well. After incubating in CHO media for 4 days, cells are loaded with 5 μCi of ^3H -myoinositol in 1 ml of media per well by overnight incubation. The extracellular radioactivity is removed by washing with phosphate buffered saline. LiCl is added to the well at final concentration of 10 mM with or without the test compound, and incubation is continued at 37°C for 15 min. Substance P is added to the well at final concentration of 0.3 nM to activate the human NK1R. After 30 min of incubation at 37°C, the medium is removed and 0.1 N HCl is added. Each well is sonicated at 4°C and extracted with CHCl_3 /methanol (1:1). The aqueous phase is applied to a 1 ml Dowex AG 1X8 ion exchange column. The column is washed with 0.1 N formic acid followed by 0.025 M ammonium formate-0.1 N formic acid. The inositol monophosphate is eluted with 0.2 M ammonium

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formate-0.1 N formic acid and quantitated by beta counter.

The data in Table 1 were obtained for compounds of formula (I):

5

TABLE 1SUBSTANCE P ANTAGONISM RESULTS

10	Compound of Ex #	IC ₅₀ @ NKIR (nM)
	1	350
	2 (Isomer A)	700
15	2 (Isomer B)	300
	3 (Isomer A)	>1 μ M
20	3 (Isomer B)	350
	4	20
	5 (Isomer A)	190
25	5 (Isomer B)	500
	6 (Isomer A)	500
30	6 (Isomer B)	30
	7	200
	8	3
35	9	30
	10	40
40	11	15
	12	10
	13	14
45	14 (Isomer A)	200
	14 (Isomer B)	300

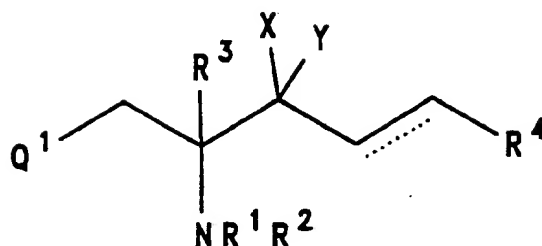
- 43 -

	15	40
	16	2
5	17	0.4
	18	0.6
10	19	2
	20	2

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CLAIMS:

1. A compound of formula (I):



(I)

15 wherein

Q¹ represents a phenyl group substituted by one or more halo; optionally substituted naphthyl; optionally substituted indolyl; optionally substituted benzthiophenyl; optionally substituted benzofuranyl; optionally substituted benzyl; or optionally substituted fluorenyl;

the dotted line represents an optional covalent bond;

one of X and Y represents H and the other of X and Y represents hydroxy or C₁₋₆alkoxy, or X and Y together form a group =O or =NOR⁵ where R⁵ is H or C₁₋₆alkyl;

R¹ and R² each independently represent H; C₁₋₆alkyl optionally substituted by hydroxy, cyano, COR^c, CO₂R^c, CONR^cR^d, or NR^cR^d (where R^c and R^d each independently represent H, C₁₋₆alkyl or phenyl(C₀₋₄alkyl) optionally substituted in the phenyl ring by one or more of C₁₋₆alkyl, C₁₋₆alkoxy, halo and trifluoromethyl); phenyl(C₁₋₄alkyl) (optionally substituted in the phenyl

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ring by one or more of C₁₋₆alkyl, C₁₋₆alkoxy, halo and trifluoromethyl); COR^C; CO₂R^C; CONR^CR^d; COC₁₋₆alkylNR^CR^d; CONR^CCOOR^d; or SO₂R^C; where R^C and R^d are as above defined;

5 R³ represents H, C₁₋₆alkyl or C₂₋₆alkenyl; and
 R⁴ represents phenyl optionally substituted by
1, 2, or 3 groups selected from C₁₋₆alkyl, C₂₋₆alkenyl,
C₂₋₆alkynyl, halo, cyano, nitro, trifluoromethyl,
trimethylsilyl, OR^a, SR^a, SOR^a, NR^aR^b, NR^aCOR^b, NR^aCO₂R^b,
10 CO₂R^a and CONR^aR^b, where R^a and R^b independently
represent H, C₁₋₆alkyl, phenyl or trifluoromethyl; or a
salt or prodrug thereof.

2. A compound as claimed in claim 1 wherein
15 R³ is H or C₁₋₆alkyl.

3. A compound as claimed in claim 1 or claim
2 wherein R¹ and R² are selected from H, COR^C and
COC₁₋₆alkylNR^CR^d.

20

4. A compound as claimed in any preceding
claim wherein the optional covalent bond is absent.

5. A compound as claimed in any preceding
25 claim wherein X and Y together represent =O.

6. A compound as claimed in any preceding
claim wherein R⁴ is 3,5-disubstituted phenyl.

30 7. A compound as claimed in any preceding
claim wherein Q¹ is 3-indolyl.

8. A compound as claimed in claim 1 selected
from:

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- 2-acetamido-1-(3-benzo[b]thienyl)-5-(3,5-bistrifluoromethylphenyl)-4-penten-3-one;
2-acetamido-1-(3-benzo[b]thienyl)-5-(3,5-bistrifluoromethylphenyl)-4-penten-3-ol;
5 2-acetamido-1-(3-benzo[b]thienyl)-5-(3,5-bistrifluoromethylphenyl)-3-methoxy-4-pentene;
2-acetamido-1-(3-benzo[b]thienyl)-5-(3,5-bistrifluoromethylphenyl)-3-pentanone;
10 2-acetamido-1-(3-benzo[b]thienyl)-5-(3,5-bistrifluoromethylphenyl)-3-pentanol;
2-acetamido-1-(3-benzo[b]thienyl)-5-(3,5-bistrifluoromethylphenyl)-3-methoxypentane;
2-acetamido-5-(3,5-bistrifluoromethylphenyl)-1-(3-indolyl)-4-penten-3-one;
15 2-acetamido-5-(3,5-bistrifluoromethylphenyl)-1-(3-indolyl)-3-pentanone;
1-(3-benzo[b]thienyl)-5-(3,5-bistrifluoromethylphenyl)-2-(N,N-dimethylglycinamido)-3-pentanone;
5-(3,5-bistrifluoromethylphenyl)-2-t-butyloxycarbonyl
20 amino-1-(3-indolyl)-3-pentanone;
2-amino-5-(3,5-bistrifluoromethylphenyl)-1-(3-indolyl)-3-pentanone;
5-(3,5-bistrifluoromethylphenyl)-2-(N,N-dimethylglycinamido)-1-(3-indolyl)-3-pentanone;
25 2-benzamido-5-(3,5-bistrifluoromethylphenyl)-1-(3-indolyl)-3-pentanone;
2-acetamido-1-(3-benzo[b]thienyl)-5-(3,5-bistrifluoromethylphenyl)-3-oximinopentane;
2-acetamido-5-(3,5-bistrifluoromethylphenyl)-1-(3,4-dichlorophenyl)-3-pentanone;
30 5-(3,5-bistrifluoromethylphenyl)-2-(3-N,N-dimethylaminopropionamido)-1-(3-indolyl)-3-pentanone;
5-(3,5-bistrifluoromethylphenyl)-2-(4-(N,N-dimethylaminobutyramido)-1-(3-indolyl)-3-pentanone;

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5-(3,5-bistrifluoromethylphenyl)-2-(5-(N,N-dimethylamino)pentanamido)-1-(3-indolyl)-3-pentanone;
 5-(3,5-bistrifluoromethylphenyl)-2-(cyclopropylcarboxamido)-1-(3-indolyl)-3-pentanone;
 5 5-(3,5-bistrifluoromethylphenyl)-2-(3-phenylbutyramido)-1-(3-indolyl)-3-pentanone;
 and salts and prodrugs thereof.

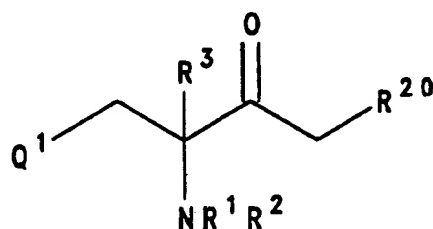
9. A compound as claimed in any preceding
 10 claim for use in therapy.

10. A pharmaceutical composition comprising a
 compound as claimed in any of claims 1 to 8 in
 association with a pharmaceutically acceptable carrier.

15

11. A process for the preparation of a
 compound as claimed in claim 1 which process comprises
 reacting an aldehyde of formula R^4CHO , wherein R^4 is as
 defined for formula (I) with a compound of formula (II):

20



(II)

wherein Q^1 , R^1 , R^2 and R^3 are as defined for formula (I)
 30 and R^{20} represents a group PR^X_3 or $PO(OR^X)_2$, wherein R^X
 represents phenyl or C_{1-10} alkyl, in the presence of a
 base, and, if necessary, converting the compound of
 formula (I) so prepared into another compound of formula
 (I), or a salt of prodrug thereof.

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12. A method for the treatment or prevention
of a physiological disorder associated with an excess of
tachykinins, which method comprises administration to a
5 patient in need thereof of a tachykinin-reducing amount
of a compound according to claim 1.

13. A method according to claim 12 for the
treatment or prevention of pain or inflammation.
10

14. A method according to claim 12 for the
treatment or prevention of migraine.

15. A method according to claim 12 for the
treatment or prevention of arthritis.
15

16. The use of a compound as claimed in claim
1 for the manufacture of a medicament for the treatment
of a physiological disorder associated with an excess of
tachykinins.
20

17. The use of a compound as claimed in claim
1 for the manufacture of a medicament for the treatment
of pain or inflammation.
25

18. A compound as claimed in any of claims 1
to 8 when prepared by the process of claim 11.

19. A process for preparing a composition as
claimed in claim 10 which process comprises bringing a
compound as claimed in any of claims 1 to 8 into
association with a pharmaceutically acceptable carrier or
excipient.
30

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20. A compound, composition or process as claimed in any one of the preceding claims, substantially as herein before described.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 93/00411

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC		
Int.Cl. 5 C07D333/58; A61K31/38;	C07D209/16; A61K31/40	C07D307/81; A61K31/34
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.Cl. 5	C07D	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
A	EP,A,0 134 578 (KAKEN PHARMACEUTICAL) 20 March 1985 see page 1 - page 5; claims ---	1,9
A	EP,A,0 333 174 (FUJISAWA PHARMACEUTICAL) 20 September 1989 see claims -----	1,9,16
<p>¹⁰ Special categories of cited documents :¹⁰</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"A" document member of the same patent family</p>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
03 JUNE 1993	17. 06. 93	
International Searching Authority	Signature of Authorized Officer	
EUROPEAN PATENT OFFICE	FRANCOIS J.C.	

INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB93/00411

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
"Remark: Although claim 12 - 15 are directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the attributed effects of the compound/composition!"
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.**

GB 9300411
SA 70667

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

03/06/93

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0134578	20-03-85	JP-A- 60058965	05-04-85
		DE-A- 3471303	23-06-88
		US-A- 4608438	26-08-86

EP-A-0333174	20-09-89	AU-A- 3132489	21-09-89
		JP-A- 1287095	17-11-89
		US-A- 5187156	16-02-93

EPO FORM P0079

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82